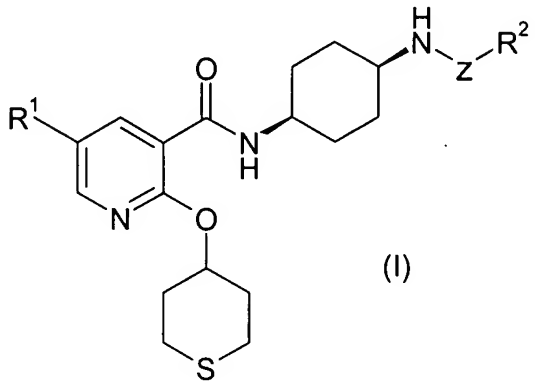
-Amendment to the Claims-

1. (Currently amended) A compound of formula (I) [[:]] ,



(I)

or a pharmaceutically acceptable salt or solvate thereof,

wherein :

R^1 is ~~selected from~~ H, halo ~~and~~ or $(C_1\text{-}C_4)$alkyl;

Z is ~~a linker group selected from~~ CO ~~and~~ or SO_2;

R^2 is ~~selected from~~ phenyl, benzyl, naphthyl, heteroaryl ~~and~~ or $(C_3\text{-}C_8)$cycloalkyl,

each of which is optionally substituted independently with ~~1~~ one to ~~3~~ three ~~substituents each independently selected from halo, CN, $CONR^3R^4$, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl OH, hydroxy$(C_1\text{-}C_6)$alkyl, $((C_3\text{-}C_8)$cycloalkyl$)\text{-}(C_1\text{-}C_6)$alkyl, phenyl (optionally substituted by OH and/or halo) $(C_3\text{-}C_8)$cycloalkyl, and NR^3R^4;~~

halo; CN; $CONR^3R^4$; $(C_1\text{-}C_6)$alkyl optionally substituted with one to three halo; OH; hydroxy$(C_1\text{-}C_6)$alkyl; $((C_3\text{-}C_8)$cycloalkyl$)\text{-}(C_1\text{-}C_6)$alkyl; phenyl optionally substituted independently with one to three hydroxy or halo; $(C_3\text{-}C_8)$cycloalkyl; or NR^3R^4; and

R^3 and R^4 are each independently ~~selected from~~ H, $(C_1\text{-}C_4)$alkyl ~~and~~ or $SO_2(C_1\text{-}C_4)$alkyl ~~; and pharmaceutically acceptable salts and solvates thereof~~.

2. (Currently amended) A compound ~~, salt or solvate according to~~ of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is H, halo, CH_3 or C_2H_5.

3. (Currently amended) A compound ~~, salt or solvate according to~~ of claim 1 ~~or claim 2~~ , or a pharmaceutically acceptable salt thereof, wherein R^2 is phenyl, ~~imidazole, pyrazine, indazole, purine, quinoline, quinazoline, benzofuran, dihydrobenzofuran, benzothiadiazole, benzoxadiazole, pyrazole, imidazopyridine,~~

~~benzimidazole, pyrazolopyridine, pyrazolopyrimidine,~~ imidazolyl, pyrazinyl, indazolyl, purinyl, quinolinyl, quinazolinyl, benzofuranyl, dihydrobenzofuranyl, benzothiadiazolyl, benzoxadiazolyl, pyrazolyl, imidazopyridyl, benzimidazolyl, pyrazolopyridyl, pyrazolopyrimidyl, benzyl or cyclopropyl, each of which is optionally substituted independently with ~~1~~ one to ~~3~~ three ~~substituents each independently selected from halo, CN, $CONR^3R^4$, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, OH, hydroxy(C_1-C_6)alkyl, $((C_3-C_8)$cycloalkyl$)-(C_1-C_6)$alkyl, phenyl (optionally substituted by OH and/or halo), (C_3-C_8)cycloalkyl, and NR^3R^4~~ halo; CN; $CONR^3R^4$; (C_1-C_6)alkyl optionally substituted with one to three halo; OH; hydroxy(C_1-C_6)alkyl; $((C_3-C_8)$cycloalkyl$)-(C_1-C_6)$alkyl; phenyl optionally substituted independently with one to three hydroxy or halo; (C_3-C_8)cycloalkyl; or NR^3R^4.

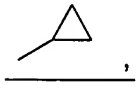
4. (Currently amended) A compound ~~, salt or solvate according to~~ of claim 1, ~~2 or 3~~ or a pharmaceutically acceptable salt thereof, wherein R^1 is H, F, Cl or CH_3.

5. (Currently amended) A compound ~~,salt or solvate according to any one of claims~~ of claim 1, ~~2, 3 or 4~~ or a pharmaceutically acceptable salt thereof, wherein R^2 is phenyl, ~~imidazole, indazole, quinoline, quinazoline, dihydrobenzofuran, benzothiadiazole, benzoxadiazole, pyrazole, imidazopyridine, benzimidazole, pyrazolopyridine,~~ imidazolyl, indazolyl, quinolyl, quinazolinyl, dihydrobenzofuranyl, benzothiadiazolyl, benzoxadiazolyl, pyrazolyl, imidazopyridyl, benzimidazolyl, pyrazolopyridyl, benzyl or cyclopropyl, each of which is optionally substituted independently with ~~by~~ one ~~or more substituents selected from~~ to three CH_3, $N(CH_3)SO_2CH_3$, $NHSO_2CH_2CH_3$, $NHSO_2CH(CH_3)_2$, OH, CH_2OH, Cl, F, C_2H_5, $CH(CH_3)_2$, C_2H_4OH, or CF_3.

6. (Currently amended) A compound ~~, salt or solvate according to any one of claims~~ of claim 1 ~~to 5~~ , or a pharmaceutically acceptable salt thereof, wherein R^1 is F.

7. (Currently amended) A compound ~~, salt or solvate according to any one of claims~~ of claim 1 ~~to 6~~ , or a pharmaceutically acceptable salt thereof, wherein Z is CO.

8. (Currently amended) A compound ~~, salt or solvate according to any one of claims~~ of claim 1 ~~to 7~~ , or a pharmaceutically acceptable salt thereof, wherein R^2 is ~~as defined in the Examples~~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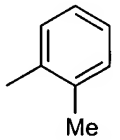
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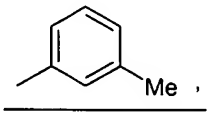
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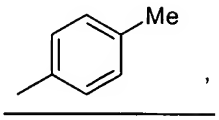
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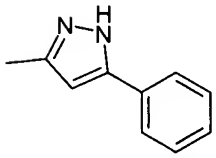
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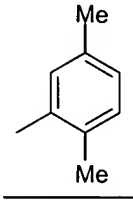
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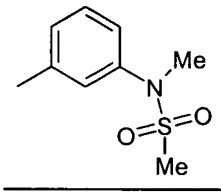
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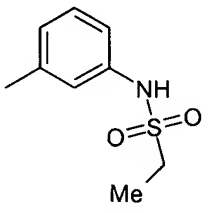
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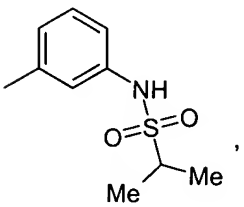
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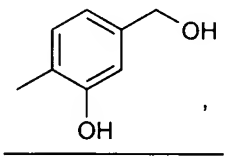
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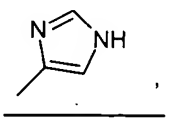
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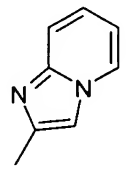
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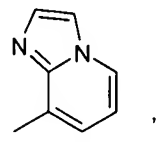
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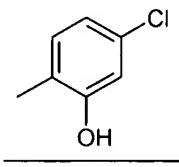
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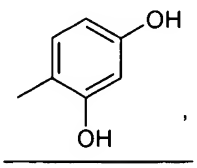
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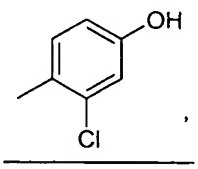
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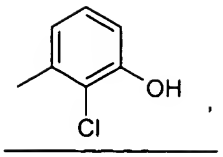
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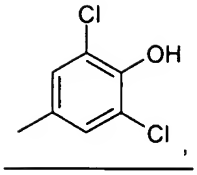
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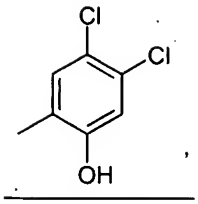
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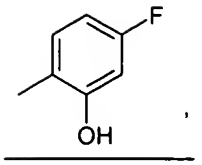
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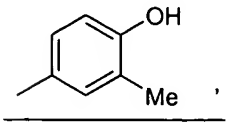
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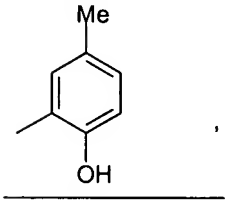
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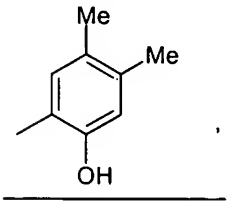
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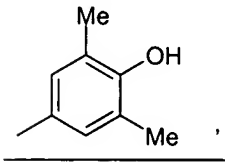
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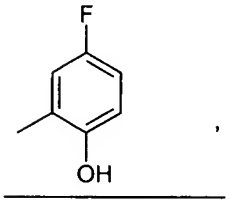
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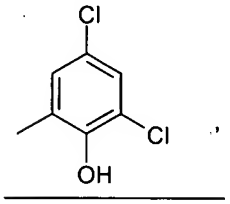
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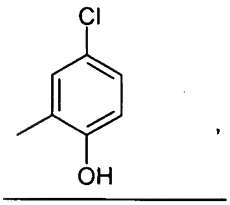
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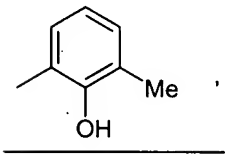
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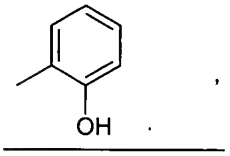
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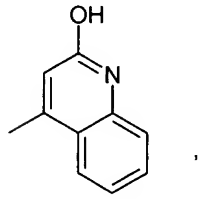
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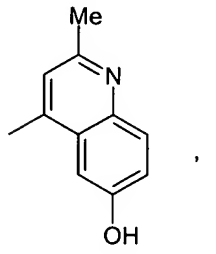
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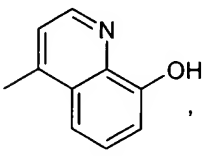
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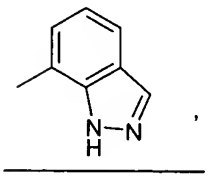
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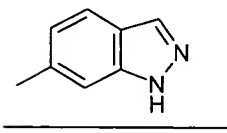
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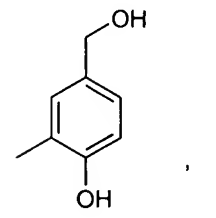
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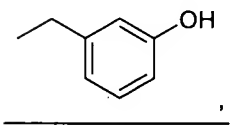
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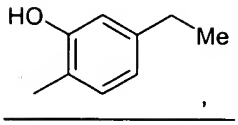
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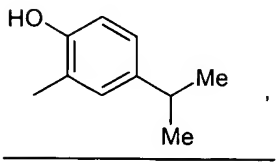
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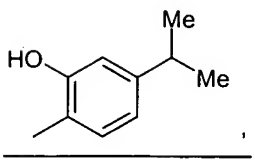
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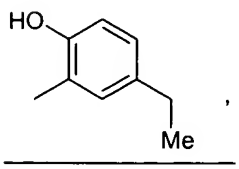
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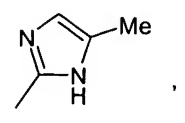
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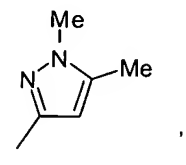
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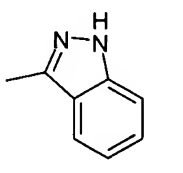
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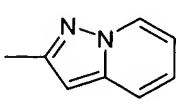
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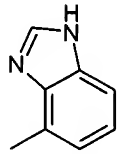
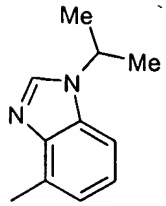
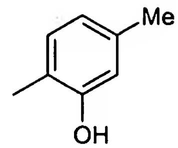
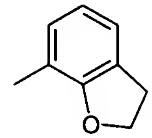
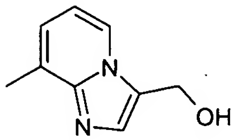
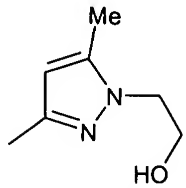
 ,

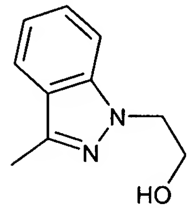
 ,

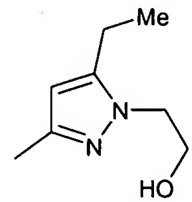
 ,

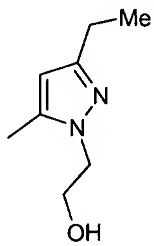
 ,

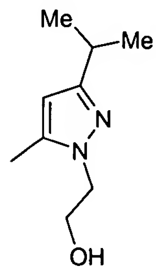
 ,

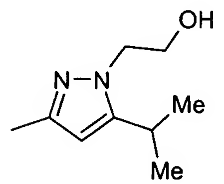
 ,

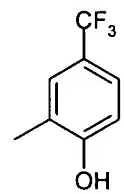
 ,

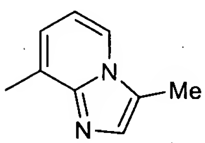
 ,

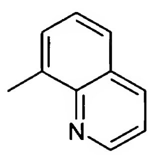
 ,

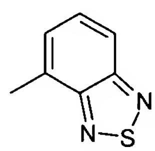
 ,

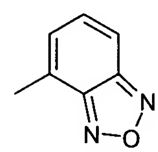
 ,

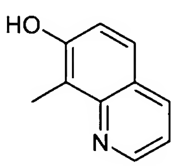
 ,

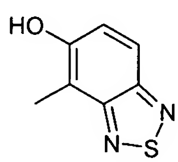
 ,

 ,

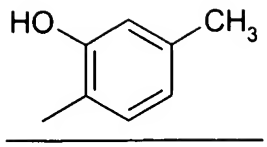
 ,

 ,

 or

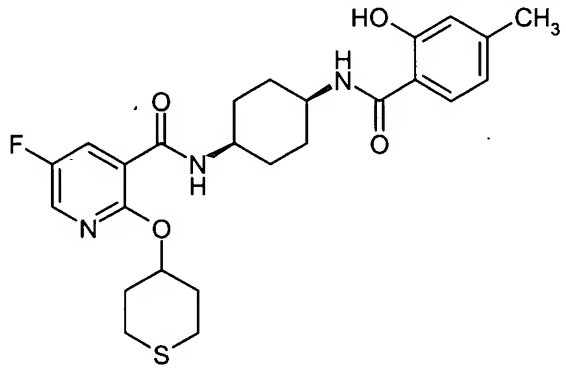
 .

9. (Currently amended) A compound ~~, salt or solvate according to any one of claims~~ of claim 1 ~~to 8~~ , or a pharmaceutically acceptable salt thereof, wherein R^2 is ~~as defined in the Example 63~~



10. (Currently amended) A compound ~~according to~~ of claim ~~1 selected from any of the Examples, or a pharmaceutically acceptable salt or solvate thereof~~ 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is fluoro, and Z is CO.

11. (Original) *Syn*-5-Fluoro-N-[4-(2-hydroxy-4-methyl-benzoylamino)-cyclohexyl]-2-(tetrahydro-thiopyran-4-yloxy)-nicotinamide of formula :

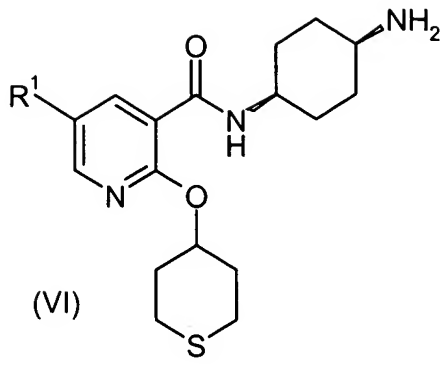


or a pharmaceutically acceptable salt or solvate thereof.

12. (Currently amended) A pharmaceutical composition comprising a compound ~~according to any one of claims~~ of claim 1 ~~to 11~~ , or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

13. - 19. (Canceled)

20. (Currently amended) A process ~~to make~~ for preparing a compound of ~~formula (I) as defined in~~ claim 1, comprising reacting ~~reaction of~~ a compound of formula (VI) ~~with a reagent of formula Y-Z-R^2~~ ,



(VI)

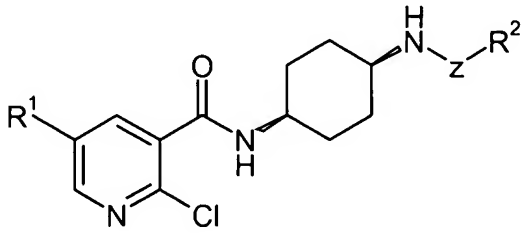
with a reagent of formula Y-Z-R^2,

wherein ~~R^1, R^2 and Z are as defined in claim 1,~~

R^1 is H, halo or $(C_1$-$C_4)$alkyl;
Z is CO or SO_2;
R^2 is phenyl, benzyl, naphthyl, heteroaryl or $(C_3$-$C_8)$cycloalkyl,
each of which is optionally substituted independently with one to three halo; CN; $CONR^3R^4$; $(C_1$-$C_6)$alkyl optionally substituted with one to three halo; hydroxy; hydroxy$(C_1$-$C_6)$alkyl; $((C_3$-$C_8)$cycloalkyl)-$(C_1$-$C_6)$alkyl; phenyl optionally substituted independently with one to three hydroxy or halo; $(C_3$-$C_8)$cycloalkyl; or NR^3R^4; and
R^3 and R^4 are each independently H, $(C_1$-$C_4)$alkyl or $SO_2(C_1$-$C_4)$alkyl;

and Y is a leaving group.

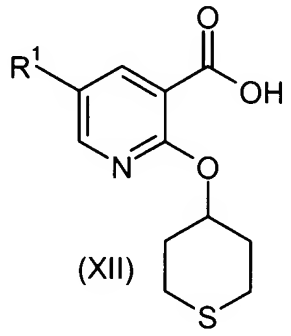
21. (Currently amended) A process ~~to make~~ for preparing a compound of ~~formula (I) as defined in~~ claim 1, comprising reacting ~~reaction of~~ a compound of formula (IX),



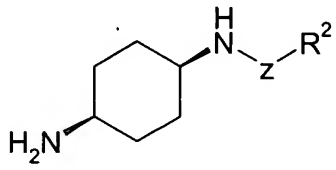
(IX)

with tetrahydrothiopyran-4-ol.

22. (Currently amended) A process ~~to make~~ for preparing a compound of ~~formula (I) as defined in~~ claim 1, comprising reacting ~~reaction of~~ a compound of formula (XII) with a compound of formula (VIII) :

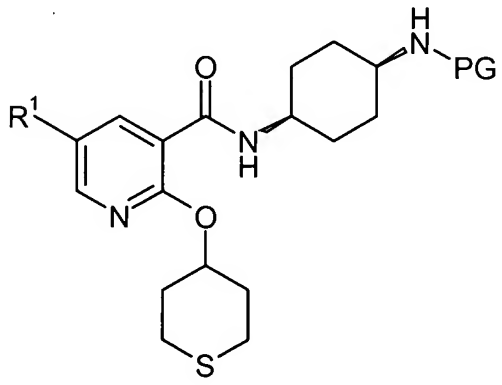


(XII)



(VIII)

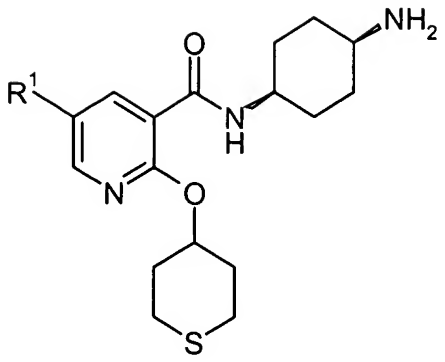
23. (Currently amended) A compound of formula (V) :



(V)

wherein R^1 is ~~as defined in claim 1~~ H, halo or $(C_1$-$C_4)$alkyl; and
PG is an amine protecting group.

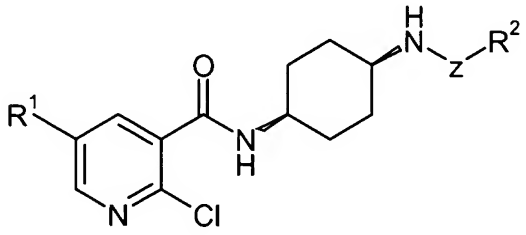
24. (Currently amended) A compound of formula (VI),



(VI)

wherein R^1 is ~~as defined in claim 1~~ H, halo or $(C_1$-$C_4)$alkyl.

25. (Currently amended) A compound of formula (IX),



(IX)

wherein ~~R^1, R^2 and Z are as defined in claim 1~~

R^1 is H, halo or $(C_1$-$C_4)$alkyl;

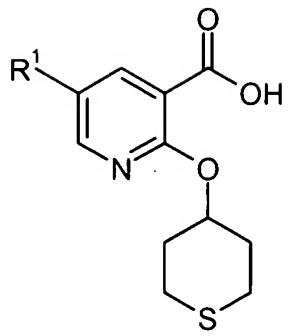
Z is CO or SO_2;

R^2 is phenyl, benzyl, naphthyl, heteroaryl or $(C_3$-$C_8)$cycloalkyl,

each of which is optionally substituted independently with one to three halo; CN; $CONR^3R^4$; $(C_1$-$C_6)$alkyl optionally substituted with one to three halo; hydroxy; hydroxy$(C_1$-$C_6)$alkyl; $((C_3$-$C_8)$cycloalkyl)-$(C_1$-$C_6)$alkyl; phenyl optionally substituted independently with one to three hydroxy or halo; $(C_3$-$C_8)$cycloalkyl; or NR^3R^4; and

R^3 and R^4 are each independently H, $(C_1$-$C_4)$alkyl or $SO_2(C_1$-$C_4)$alkyl.

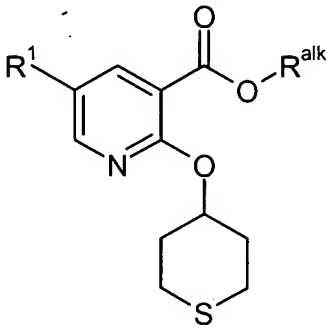
26. (Currently amended) A compound of formula (XII),



(XII)

R^1 is ~~as defined in claim 1~~ H, halo or (C_1-C_4)alkyl.

27. (Currently amended) A compound of formula (XI),



(XI)

wherein R^1 is ~~as defined in claim 1~~ H, halo or (C_1-C_4)alkyl; and R^{alk} ~~represents~~ is (C_1-C_4)alkyl.

28. (Currently amended) A combination ~~of~~ comprising a compound ~~according to any one of claims~~ of claim 1 ~~to 11~~ with ~~other~~ another therapeutic ~~agents~~ agent selected from :

(a) 5-Lipoxygenase (5-LO) inhibitors or 5-lipoxygenase activating protein (FLAP) antagonists,

(b) Leukotriene antagonists (LTRAs) including antagonists of LTB4, LTC4, LTD4, and LTE4,

(c) Histaminic receptor antagonists including H1, H3 and H4 antagonists,

(d) α1- and α2-adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use,

(e) Muscarinic M3 receptor antagonists or anticholinergic agents,

(f) β2-adrenoceptor agonists,
(g) Theophylline,
(h) Sodium cromoglycate,
(i) COX-1 inhibitors (NSAIDs) and COX-2 selective inhibitors,
(j) Oral or inhaled Glucocorticosteroids,
(k) Monoclonal antibodies active against endogenous inflammatory entities,
(l) Anti-tumor necrosis factor (anti-TNF-a) agents,
(m) Adhesion molecule inhibitors including VLA-4 antagonists,
(n) Kinin-B1 - and B2 -receptor antagonists,
(o) Immunosuppressive agents,
(p) Inhibitors of matrix metalloproteases (MMPs),
(q) Tachykinin NK1, NK2 and NK3 receptor antagonists,
(r) Elastase inhibitors,
(s) Adenosine A2a receptor agonists,
(t) Inhibitors of urokinase,
(u) Compounds that act on dopamine receptors, e.g. D2 agonists,
(v) Modulators of the NFkb pathway, e.g. IKK inhibitors,
(w) Agents that can be classed as mucolytics or anti-tussive,
(x) antibiotics, and
(y) p38 MAP kinase inhibitors.

29. (New) A method of treating a disease, disorder or condition in which PDE4 inhibition is beneficial in a mammal suffering from a disease, disorder or condition in which PDE4 inhibition is beneficial, said method comprising administering to said mammal in need of such treatment a therapeutically effective amount of a compound of claim 1, a pharmacuetically acceptable salt thereof or a pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent or excipient.

30. (New) A method of claim 29, wherein the disease, disorder or condition is selected from

- asthma of whatever type, etiology, or pathogenesis, in particular asthma that is a member selected from the group consisting of atopic asthma, non-atopic asthma, allergic asthma, atopic bronchial IgE-mediated asthma, bronchial

asthma, essential asthma, true asthma, intrinsic asthma caused by pathophysiologic disturbances, extrinsic asthma caused by environmental factors, essential asthma of unknown or inapparent cause, non-atopic asthma, bronchitic asthma, emphysematous asthma, exercise-induced asthma, allergen induced asthma, cold air induced asthma, occupational asthma, infective asthma caused by bacterial, fungal, protozoal, or viral infection, non-allergic asthma, incipient asthma and wheezy infant syndrome,

- chronic or acute bronchoconstriction, chronic bronchitis, small airways obstruction, and emphysema,
- obstructive or inflammatory airways diseases of whatever type, etiology, or pathogenesis, in particular an obstructive or inflammatory airways disease that is a member selected from the group consisting of chronic eosinophilic pneumonia, chronic obstructive pulmonary disease (COPD), COPD that includes chronic bronchitis, pulmonary emphysema or dyspnea associated therewith, COPD that is characterized by irreversible, progressive airways obstruction, adult respiratory distress syndrome (ARDS) and exacerbation of airways hyper-reactivity consequent to other drug therapy
- pneumoconiosis of whatever type, etiology, or pathogenesis, in particular pneumoconiosis that is a member selected from the group consisting of aluminosis or bauxite workers' disease, anthracosis or miners' asthma, asbestosis or steam-fitters' asthma, chalicosis or flint disease, ptilosis caused by inhaling the dust from ostrich feathers, siderosis caused by the inhalation of iron particles, silicosis or grinders' disease, byssinosis or cotton-dust asthma and talc pneumoconiosis;
- bronchitis of whatever type, etiology, or pathogenesis, in particular bronchitis that is a member selected from the group consisting of acute bronchitis, acute laryngotracheal bronchitis, arachidic bronchitis, catarrhal bronchitis, croupus bronchitis, dry bronchitis, infectious asthmatic bronchitis, productive bronchitis, staphylococcus or streptococcal bronchitis and vesicular bronchitis,
- bronchiectasis of whatever type, etiology, or pathogenesis, in particular bronchiectasis that is a member selected from the group consisting of cylindric bronchiectasis, sacculated bronchiectasis, fusiform bronchiectasis, capillary bronchiectasis, cystic bronchiectasis, dry bronchiectasis and follicular bronchiectasis,
- seasonal allergic rhinitis or perennial allergic rhinitis or sinusitis of whatever type, etiology, or pathogenesis, in particular sinusitis that is a member selected

from the group consisting of purulent or nonpurulent sinusitis, acute or chronic sinusitis and ethmoid, frontal, maxillary, or sphenoid sinusitis,

- rheumatoid arthritis of whatever type, etiology, or pathogenesis, in particular rheumatoid arthritis that is a member selected from the group consisting of acute arthritis, acute gouty arthritis, chronic inflammatory arthritis, degenerative arthritis, infectious arthritis, Lyme arthritis, proliferative arthritis, psoriatic arthritis and vertebral arthritis,
- gout, and fever and pain associated with inflammation,
- an eosinophil-related disorder of whatever type, etiology, or pathogenesis, in particular an eosinophil-related disorder that is a member selected from the group consisting of eosinophilia, pulmonary infiltration eosinophilia, Loffler's syndrome, chronic eosinophilic pneumonia, tropical pulmonary eosinophilia, bronchopneumonic aspergillosis, aspergilloma, granulomas containing eosinophils, allergic granulomatous angiitis or Churg-Strauss syndrome, polyarteritis nodosa (PAN) and systemic necrotizing vasculitis,
- atopic dermatitis, allergic dermatitis, contact dermatitis, or allergic or atopic eczema,
- urticaria of whatever type, etiology, or pathogenesis, in particular urticaria that is a member selected from the group consisting of immune-mediated urticaria, complement-mediated urticaria, urticariogenic material-induced urticaria, physical agent-induced urticaria, stress-induced urticaria, idiopathic urticaria, acute urticaria, chronic urticaria, angioedema, cholinergic urticaria, cold urticaria in the autosomal dominant form or in the acquired form, contact urticaria, giant urticaria and papular urticaria,
- conjunctivitis of whatever type, etiology, or pathogenesis, in particular conjunctivitis that is a member selected from the group consisting of actinic conjunctivitis, acute catarrhal conjunctivitis, acute contagious conjunctivitis, allergic conjunctivitis, atopic conjunctivitis, chronic catarrhal conjunctivitis, purulent conjunctivitis and vernal conjunctivitis,
- uveitis of whatever type, etiology, or pathogenesis, in particular uveitis that is a member selected from the group consisting of inflammation of all or part of the uvea, anterior uveitis, iritis, cyclitis, iridocyclitis, granulomatous uveitis, nongranulomatous uveitis, phacoantigenic uveitis, posterior uveitis, choroiditis; and chorioretinitis,
- multiple sclerosis of whatever type, etiology, or pathogenesis, in particular multiple sclerosis that is a member selected from the group consisting of primary progressive multiple sclerosis and relapsing remitting multiple sclerosis,

- autoimmune/inflammatory diseases of whatever type, etiology, or pathogenesis, in particular an autoimmune/inflammatory disease that is a member selected from the group consisting of autoimmune hematological disorders, hemolytic anemia, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, polychondritis, scleroderma, Wegner's granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Stevens-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel diseases, ulcerative colitis, endocrin opthamopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, juvenile diabetes or diabetes mellitus type I, keratoconjunctivitis sicca, epidemic keratoconjunctivitis, diffuse interstitial pulmonary fibrosis or interstitial lung fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, glomerulonephritis with and without nephrotic syndrome, acute glomerulonephritis, idiopathic nephrotic syndrome, minimal change nephropathy, inflammatory/hyperproliferative skin diseases, benign familial pemphigus, pemphigus erythematosus, pemphigus foliaceus, and pemphigus vulgaris,
- allogeneic graft rejection following organ transplantation,
- inflammatory bowel disease (IBD) of whatever type, etiology, or pathogenesis, in particular inflammatory bowel disease that is a member selected from the group consisting of collagenous colitis, colitis polyposa, transmural colitis, ulcerative colitis and Crohn's disease (CD),
- septic shock of whatever type, etiology, or pathogenesis, in particular septic shock that is a member selected from the group consisting of renal failure, acute renal failure, cachexia, malarial cachexia, hypophysial cachexia, uremic cachexia, cardiac cachexia, cachexia suprarenalis or Addison's disease, cancerous cachexia and cachexia as a consequence of infection by the human immunodeficiency virus (HIV),
- liver injury,
- pulmonary hypertension of whatever type, etiology or pathogenesis including primary pulmonary hypertension / essential hypertension, pulmonary hypertension secondary to congestive heart failure, pulmonary hypertension secondary to chronic obstructive pulmonary disease, pulmonary venous hypertension, pulmonary arterial hypertension and hypoxia-induced pulmonary hypertension,
- bone loss diseases, primary osteoporosis and secondary osteoporosis,
- central nervous system disorders of whatever type, etiology, or pathogenesis, in particular a central nervous system disorder that is a member selected from the

group consisting of depression, Alzheimers disease, Parkinson's disease, learning and memory impairment, tardive dyskinesia, drug dependence, arteriosclerotic dementia and dementias that accompany Huntington's chorea, Wilson's disease, paralysis agitans, and thalamic atrophies,

- infection, especially infection by viruses wherein such viruses increase the production of TNF-α in their host, or wherein such viruses are sensitive to upregulation of TNF-α in their host so that their replication or other vital activities are adversely impacted, including a virus which is a member selected from the group consisting of HIV-1, HIV-2, and HIV-3, cytomegalovirus (CMV), influenza, adenoviruses and Herpes viruses including *Herpes zoster* and *Herpes simplex*,
- yeast and fungus infections wherein said yeast and fungi are sensitive to upregulation by TNF-α or elicit TNF-α production in their host, e.g., fungal meningitis, particularly when administered in conjunction with other drugs of choice for the treatment of systemic yeast and fungus infections, including but are not limited to, polymixins, e.g. Polymycin B, imidazoles, e.g. clotrimazole, econazole, miconazole, and ketoconazole, triazoles, e.g. fluconazole and itranazole as well as amphotericins, e.g. Amphotericin B and liposomal Amphotericin B,
- ischemia-reperfusion injury, ischemic heart disease, autoimmune diabetes, retinal autoimmunity, chronic lymphocytic leukemia, HIV infections, lupus erythematosus, kidney and ureter disease, urogenital and gastrointestinal disorders and prostate diseases,
- scar formation in the human or animal body, such as scar formation in the healing of acute wounds, and
- psoriasis, other dermatological and cosmetic uses, including antiphlogistic, skin-softening, skin elasticity and moisture-increasing activities.

31. A method of claim 30 wherein the disease, disorder or condition is chronic obstructive pulmonary disease, asthma, or chronic bronchitis.